

# Three secondary malignant neoplasms in a childhood cancer survivor positive for nibrin gene mutation – a case report and literature review

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Childhood cancer survivors often develop subsequent neoplasms secondary to radio- (RT) or chemotherapy (CHT). Risk factors for the secondary tumors are the female gender, older age at diagnosis, Hodgkin's lymphoma treatment and the use of RT. The cumulative incidence of the second malignant neoplasm, excluding non-melanoma skin cancer, 30 years after the childhood cancer diagnosis is around 8% [1]. We present the case of a patient who developed three independent malignancies following radical treatment of nephroblastoma (Wilms' tumor; WT) in childhood, found at the age of 53 to be a carrier of the 657\_661delACAAA (p. Lys219fs) mutation in the 6/16 exon of the nibrin coding gene (NBN).

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## Case report

A 52-year-old woman was diagnosed with hepatic hilum lymphadenopathy in November 2016. Past medical history of the patient included two metachronic neoplasms: WT with peritoneal infiltration at the age of six years treated with left nephrectomy followed by CHT with actinomycin D and left flank RT at the dose of 35.2 Gy, and grade III adenocarcinoma of the descending colon treated with left hemicolectomy at the age of 26 years. The family history was unremarkable.

At admission, physical examination was unremarkable. The patient's performance status ECOG was 0. Magnetic resonance imaging (MR of 08.2016) showed the presence of a very small (11 x 13 mm) lymph node with low radiotracer uptake (SUV 2.1) at the positron emission tomography scan with 18-fluorodeoxyglucose. Six months later, MR showed a significant progression of the lesion (35 x 22 mm). The ul-

trasound-guided core-needle biopsy proved the diagnosis of a grade II leiomyosarcoma. In April 2017, the tumor originating from vena cava inferior was removed. Despite the presence of tumor cells in the resection margin adjuvant treatment was not administered due to the hemorrhagic complications and prolonged postoperative recovery. Eight months later, the patient was diagnosed with undifferentiated ovarian cancer, stage IA, and treated with radical surgery followed by 6 cycles of adjuvant CHT (carboplatin and paclitaxel).

Genetic testing after the diagnosis of sarcoma showed that the patient was a carrier of the 657\_661delACAAA (p. Lys219fs) mutation in the 6/16 exon of the nibrin coding gene (NBN), uncommon in the Polish population. The leiomyosarcoma specimen examined for the presence of potentially targetable mutations using Archer FusionPlex CTL panel (ArcherDX) did not yield any hits.

## Jak cytować:

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## Discussion

Each year about 1000 children in Poland are diagnosed with cancer [2], including about 60 cases of the most common kidney tumor – WT [3]. Multimodal therapy including surgery with perioperative CHT and adjuvant RT in high-risk tumors results in 90% 5-year overall survival in localized disease and 75% at the metastatic stage [4].

However, children who underwent RT or CHT are at significantly higher risk of subsequent neoplasms compared to the general population [1, 5, 6]. To decrease the risk of secondary malignancies RT, it is recommended only for high-risk groups, with low total doses and minimal exposure of adjacent organs. In consequence, the incidence rates of secondary malignancies in the subsequent decades have decreased, yet the risk is still higher than in the general population [5].

The cumulative incidence of a secondary malignancy in WT survivors is 0.6% at 10 years, 1.6% at 20 years and 3.8% at 30 years after the initial diagnosis [6]. The most common secondary malignancies include colon cancer (SIR 14.1 95% CI 1.7–51.1), soft tissue sarcoma (SIR 11.4 95% CI 2.4–33.4), liver cancer (SIR 34.7 95% CI 4.2–125.5) and thyroid cancer (SIR 4.4 95% CI 1.2–11.3) [6]. Overall survival for patients with subsequent malignancies is 64.5% at 5 years [6].

In the presented case, the development of the left-sided colon cancer 20 years after initial diagnosis of WT was typical, although the age of 26 years at diagnosis is much below the median age of colon cancer occurrence [2, 5, 6]. Long-term follow-up showed that the surgical resection was curative. However, 45 years after WT treatment the patient developed another neoplasm – leiomyosarcoma of the inferior vena cava. Vascular leiomyosarcomas account for about 2% of adult soft tissue sarcomas, most frequently in 50–60-year-old women [7]. The most common location is inferior vena cava. About 400 cases have been reported in the literature to date, none of which was secondary to the childhood cancer therapy. Due to the rarity of the disease, an optimal treatment has not been established [7].

The presented patient did not receive any adjuvant treatment because of serious postoperative complications. Ovarian cancer diagnosed shortly afterwards as the third subsequent malignancy was typical, regarding the latency period, for radiation-induced solid tumors [5, 6]. This malignancy was treated with standard surgery followed by adjuvant CHT.

Our case is interesting for several reasons. First, despite an increased risk of subsequent neoplasms, childhood cancer survivors seldom develop multiple malignant tumors diagnosed at early stages that can be successfully managed with surgery. Second, the patient was carrying a pathogenic mutation of the NBN gene. Physiologically, the nibrin protein is important in the process of the double-strand breaks DNA repair. The biallelic defects are responsible for the Nijmegen syndrome [8]. Our patient did not present the full spectrum of Nijmegen syndrome features, but multiple malignancies after

radiotherapy in childhood are probably connected with the carried mutation. Heterozygotes for NBN mutation are also at increased risk of malignancies [9]. All of the 127 variants of the NBN gene are pathogenic. Finally, it is difficult to define the role of the NBN mutation in the development of subsequent malignancies versus the radio- and chemotherapy in childhood and frequent CT examinations. Recent epidemiological results suggested an increased cancer risk after receiving CT examinations in childhood or adolescence. The carcinogenic role of this factor is unclear due to the possible impact of other cancer predisposing factors. Nonetheless, an Australian study, with a mean follow-up of 9.5 years, reported excess risks of cancer at several sites, and an increase of about 20% in the risk of all cancers, compared with individuals not exposed to CT examination [10].

## Conclusion

The presented case exemplifies the importance of genetic counseling in childhood cancer survivors who have not been genetically tested. Wise and watchful follow-up in childhood cancer survivors allows for early diagnosis.

**Conflict of interest:** none declared

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